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CRYSTALS OF
ATROPINE METHYLNITRATE

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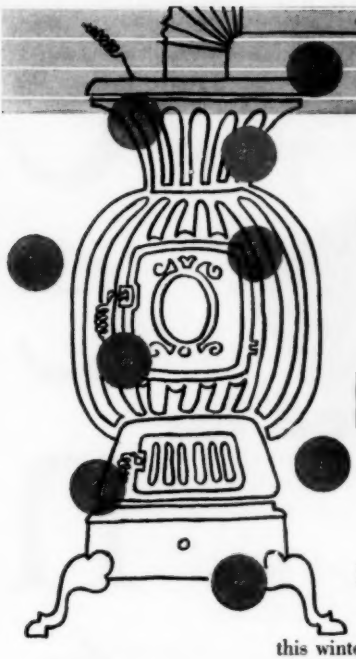

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E D I T O R I A L S

PRICE OR PROFESSION?

THE general public is more price conscious in its contact with pharmacy than with any of the other health professions. While some of this emphasis on price is unavoidable, pharmacists would do well to consider carefully some of the reasons for this attitude as well as some of its dangers.

Few people requiring surgery shop around to find a physician who will perform the operation for the lowest fee. Here the emphasis is on professional skill and reputation; the fee charged is of secondary importance. Many persons are entirely willing to pay a famed specialist ten times the usual cost of some surgical attention simply to get the best possible. The rapid growth of specialization in medicine, at the expense of the general practitioner, is ample evidence of the public demand for expert attention regardless of cost. In dentistry the same situation prevails and we have the orthodontist, the exodontist, etc., with less thought given to cost than to expertness in his specialty.

Pharmacy, however, presents a far different picture and one which becomes progressively worse as pharmacists themselves encourage price consciousness on the part of their customers. This is difficult to understand for many reasons and pharmacists, generally, should stop to consider its full implications.

If price, indeed, is the thing of paramount importance in evaluating our services to the public then we have become merchants only and it is small wonder that customers regard our only service as the bottle they receive and this the same wherever they go. So well have some pharmacists convinced the public that this is so that it is becoming common practice for a patient to "shop around" with his prescription and give it to the pharmacist quoting the lowest price. Some pharmacists try to rationalize this state of affairs by explaining that the public considers pharmaceutical service so uniformly good that it makes no difference where the prescription is filled, the same product is delivered. The truth is the public feels that no service except selling is rendered and therefore it makes no more difference where a prescription is filled than it does where one buys cigarettes. This is a sad state of affairs indeed.

Should this trend continue we may expect all sorts of damage to our professional stature as well as the loss of certain special prerogatives and privileges granted by law. Pharmacists are already being challenged by supermarkets and grocery stores which see in pharmaceuticals a lucrative side-line. While we cry for restrictive legislation our own behavior at times gives comfort and aid to our enemies who would take from us what little protection we have. Laws are passed regarding drugs not to protect the pharmacist but the public. We know they are needed but we should in our professional contacts continually act in such a way as to convince the public that such legislation gives them protection. If we operate solely on a price basis then the admission of the supermarket seems to the public a rational step and one calculated to save them even more in their purchase of drugs.

Fortunately, there are still pharmacists who look upon their profession as an opportunity of serving their community and their fellowman, and what an opportunity it really is. No practitioner in the health professions has more individual contacts than the pharmacist. The general public is ready and eager to improve its health habits, its knowledge of sanitation and to prevent disease. The new miracle drugs of pharmacy have made a profound impact on the public mind and never was there a more propitious time for pharmacists to measure up to full professional stature in the eyes of the public. The medical profession needs pharmaceutical guidance more than ever before and physicians everywhere would gladly accept us as full partners if we would but meet this challenge. Never have we had more to offer and never were we needed more.

Those who continually point the way to success in pharmacy by better merchandizing are false prophets and it would be well to consider their motives. It may improve the business of pharmacy but in this area the large operators will always in the end prevail. The real challenge of pharmacy, today, is in filling a much needed place on the public health team. When this is done, as it will be done, the public will see beyond the bottle they receive in appreciation of our service rendered. We shall no longer need fear the super-market, the grocery or the other purely business enterprises. A grateful public will see to that just as it refuses to let laymen practice medicine.

L. F. Tice

"LABORATORY NOTES"

ALL persons engaged in laboratory work, whether it be research or control, are often confronted with the decision of what should be done with information concerning some minor finding, new technique or observation. Only too frequently nothing is done to inform others of what may be a real improvement or a time saving device well worth attention. The task of preparing a formal paper replete with references may seem too great or the thing to be reported may not seem to warrant a paper in its usual sense.

A few publications, notably *Science,* have made the publication of such items possible and in doing so have rendered a valuable service. It is our wish to extend to those who read our journal a similar opportunity.

This month two short items submitted by staff members of the LaWall Memorial Laboratory of Pharmacology and Biochemistry are published. It is hoped that other workers in pharmacy or any of the related sciences will avail themselves of this opportunity. Publication will be prompt and this new section should be of value to workers in many fields.

THE PREPARATION, PROPERTIES AND THERAPEUTIC APPLICATION OF ATROPINE METHYLNITRATE

By George N. Malpass

THE physiological actions of the alkaloid atropine have long been known to physicians, pharmacologists, and pharmaceutical chemists. Its efficacy and limitations have been the subject of countless scientific articles, chapters in texts, and even volumes. McGuigan (1) states "The great drawback to the use of atropine in many cases is the undesirable actions. In all cases in which it is administered, it causes dry skin, lessened secretions, quickened heart and dilated pupil, where often these are undesirable."

The general pharmacological actions are two in number. Atropine stimulates the central nervous system, thereby causing a rise in blood pressure, flushing of face and neck, and stimulation of the respiratory center. It also paralyzes the parasympathetic cholinergic receptive mechanism. This checks secretion of saliva, gastric juice, perspiration, and nasal secretion. It allays smooth muscle spasm of neurogenic origin, and dilates the pupil of the eye, paralyzing accommodation, and raising intra-ocular tension. Atropine also accelerates the heart by vagus paralysis. Therapeutic usefulness is, therefore, limited by toxic symptoms, which in turn depend upon dosage, and the object of medication.

In the latter years of the preceding century, atropine was widely used as a mydriatic. Many atropine derivatives and atropine-like drugs were prepared in an effort to improve the action of the parent substance. In this search for improved mydriasis, the antispasmodic action was frequently overlooked.

Among the many compounds prepared was atropine methylnitrate, known also as atropine methyl nitrate, atropine methonitrate, or methylatropine nitrate.

This compound apparently acts by depressing the parasympathetic system and the vagus endings rather than by direct cerebral

stimulation. Thus the spasmolytic activity is retained, while symptoms of action on the central nervous system are greatly reduced.

Atropine methylnitrate appears to act more promptly than atropine as a mydriatic and to possess a more transient (therefore more desirable) duration of dilatation. It is, however, much weaker in action. Distributed in 1903 under the trade name "Eumydrin", it proved only moderately successful in ophthalmology (2). More recently atropine methylnitrate was shown to have significantly less mydriatic action than atropine, although the cycloplegic action was about the same (3).

Another early use of this compound was as an anhidrotic, although it was inferior to atropine for this purpose (4).

Revived by Usener (5) in 1926 for its antispasmodic value in the treatment of infant pyloric stenosis, atropine methylnitrate proved its superiority, especially following the results of a large number of cases successfully treated by Svensgaard (6). The very properties which rendered the compound inferior to atropine for mydriasis or anhidrosis permitted larger doses to be given for a spasmolytic action. Svensgaard used 0.5 mg. (1/120 gr.) five to seven times daily on infants. This was well tolerated, and the mortality reduced by 75% as compared with atropine. Other investigators began to use atropine methylnitrate in a similar manner and reported their results in the literature (7, 8, 9, 10, 11, 12).

During the past few years atropine methylnitrate has been widely employed as a substitute for atropine as a general smooth muscle spasmolytic, in such conditions as spastic colon, pylorospasm, biliary or renal colic, dysmenorrhea, peptic ulcer, ureteral or prostatic cramps, and bronchial asthma. It relaxes the gastric musculature, which has a pronounced local and insignificant general effect (13),—and therein lies the secret of its success.

There is some disagreement in the literature regarding the toxicity of atropine methylnitrate. Sollman states that its toxicity is only about 1/50 as great as atropine (14). Graham and Lazarus (15) found that the L. $D._{50}$ of atropine methylnitrate was three times as great as atropine when administered intraperitoneally to white mice. In spite of these discrepancies, clinical results demonstrate that atropine methylnitrate is an efficient antispasmodic in adult doses of 1 or 2 mg. (1/60 or 1/30 gr.) four times daily, without causing noticeable anhidrosis, dilatation of the pupil or other sign of toxicity. Occasion-

ally much larger doses have been used, without apparent untoward effects. There is general agreement in the literature that the intensity of antispasmodic action is about equal to that of atropine.

In cases requiring sedation in addition to spasmolysis, 1 mg. (1/60 gr.) atropine methylnitrate may be combined with 16 mg. (¼ gr.) of phenobarbital. This combination is of particular value for the nervous or apprehensive patient. Peptic ulcer control may be enhanced by simultaneous administration of an antispasmodic and an antacid. An effective combination is atropine methylnitrate, 1 mg. (1/60 gr.); aluminum dihydroxyaminoacetate, 227 mg. (3½ gr.); and phenobarbital, 8 mg. (⅛ gr.). One such dose will usually control the patient, while two or even three times this amount will provide relief without danger of toxic symptoms or excessive hypnosis.

Atropine methylnitrate can be administered by methods other than the oral route if desired, although this is seldom necessary since the compound is readily absorbed from the digestive tract and is rapidly effective. In cases of severe gastric disturbance a rectal irrigation may be given if desired. Soluble triturates are commercially available which can be dissolved in a small amount of water and used as an enema, thus eliminating the need for parenteral administration.

The British Pharmaceutical Codex [16] lists a preparation for local use as a spray in which atropine methylnitrate is one of the ingredients. Other combinations may suggest themselves, based on newer knowledge of this old but efficacious and versatile drug.

Preparation of Atropine Methylnitrate

Atropine methylnitrate can be prepared by reacting atropine alkaloid with methyl bromide (or methyl iodide). The addition compound atropine methylbromide is formed—the methyl and bromine linking onto the nitrogen in the atropine formula. The bromine can then be displaced with the (NO_3) radical by reacting with silver nitrate, the liberated bromine combining with the silver to form AgBr, which is precipitated.

After some preliminary experimental studies, it became evident that a satisfactory and practical method is the two-step process in which atropine is first combined with methyl bromide and subsequently reacted with silver nitrate.

Experimental

I. *Preparation of Atropine Methylbromide*

A convenient quantity of atropine alkaloid USP is dissolved in chloroform or other suitable solvent and reacted with the molecular equivalent of methyl bromide, added slowly at room temperature. The mixture is cooled in a refrigerator at 50° F. until no further crystallization occurs. The crystals of atropine methylbromide formed by this reaction are removed by filtration, washed with chloroform or ether, and dried.

A second crop can be obtained by concentrating the mother liquor and adding a slight excess of chloroform or ether. The average total yield of crude atropine methylbromide in a series of thirty (30) experiments was 93.6% of theory.

At this point, recrystallization can be undertaken if absolute purity is desired. The purified product is atropine methylbromide—$C_{16}H_{20}O_3N(CH_3)_2$ Br, M. Wt. 384.13. It is a white crystalline solid, melting at 222-223° C., freely soluble in water, slightly soluble in alcohol, and almost insoluble in chloroform or ether.

II. *Conversion of Atropine Methylbromide to Atropine Methylnitrate*

The dried atropine methylbromide previously prepared is dissolved in a small amount of freshly distilled water. To this solution is added the molecular equivalent of silver nitrate as a saturated solution, slowly and with constant stirring. The silver bromide produced is filtered off in a Büchner funnel and washed with freshly distilled water. The filtrate and washings are concentrated *in vacuo* to dryness at a temperature of 55° C. and washed several times with anhydrous ethanol to remove the last traces of water. The crude atropine methylnitrate is then dried at a low temperature and stored in a vacuum desiccator.

III. *Purification of Crude Atropine Methylnitrate*

The material produced in II. is purified by dissolving in alcohol and recrystallizing by the addition of acetone, chloroform or ether. The crystals are harvested by decantation and subsequently washed

on a Büchner funnel with further portions of acetone, chloroform, or ether. The dried product is a white, odorless, crystalline powder,—$C_{16}H_{20}O_3N(CH_3)_2NO_3$—M. W. 366.4. It is freely soluble in water, slightly soluble in alcohol, and almost insoluble in chloroform, ether, or acetone. It has a clearly defined melting point at 162-164° C. when determined by the USP or other standard methods. Repeated crystallization does not alter the melting point, indicating chemical purity. There was no difference in the melting point reading with samples dried at 37° C. and 105° C. respectively. The B. P. C. states "166-168° C. after drying at 105° C.," while other compendia use 163° C., a figure comparable with our experimental results. The highest reading obtained in a series of 30 samples tested was 164° C.

IV. *Tests and Assay*

a. *Identification tests*

(1) To a solution of atropine methylnitrate, add sodium hydroxide T. S. The alkaloidal base is not precipitated.

(2) To a few drops of diphenylamine solution, add one drop of a 1% aqueous solution of atropine methylnitrate. An intense blue color develops.

(3) Mix 10 mg. of atropine methylnitrate with 5 drops of nitric acid and evaporate to dryness on a water bath. The residue has a faint yellow color which changes to violet when moistened with a freshly prepared alcoholic solution of potassium hydroxide.

(4) To 5 cc. of a 1% aqueous solution of atropine methylnitrate, add 0.5 cc. of hydrochloric acid and 2.5 cc. of gold chloride solution. The aurichloride so formed, recrystallized from boiling water, acidified with hydrochloric acid and dried at 105° C. has a melting point of 205° C. (distinction from atropine and hyoscyamine).

b. *Tests for Impurities*

(1) *Silver*—To 1 cc. of a 10% solution of atropine methylnitrate in water, add 0.2 cc. of sodium sulfide solution. No darkening in color is produced.

To another portion, add sodium chloride solution and acidify with nitric acid. No precipitate, and not more than a faint opalescence is produced.

(2) *Halides*—To 1 cc. of a 10% solution of atropine methylnitrate in water, add 0.2 cc. of silver nitrate solution. No precipitate, and not more than a faint opalescence is produced.

(3) *Ash*—Not more than 0.1%.

(4) *Loss on drying*—When dried to constant weight at 105° C., atropine methylnitrate loses not more than 0.5% of its weight.

c. *Assay*

(1) *Nitrate nitrogen*—Dissolve 400 mg. of atropine methylnitrate in distilled water and dilute to exactly 200 cc. Then place 0.5 cc. of this solution in a 25 cc. graduated test tube, adding 2 cc. phenoldisulfonic acid reagent as the solution is cooled under running water. This mixture is allowed to stand 15 minutes. Dilute to 5 cc. with distilled water and while cooling under running water, add slowly an excess of 28% ammonia water (about 8 cc.). After the mixture is cool, dilute to exactly 25 cc. with distilled water. The color produced in this solution is compared with 0.6 cc. of a standard solution of potassium nitrate containing 0.25968 mg. KNO_3 in each 0.6 cc. solution. This is treated exactly as the first solution. This amount of standard solution is equivalent to 0.036 mg. of nitrate nitrogen or 0.041 mg. atropine methylnitrate. Color comparison is made on Lumetron Photoelectric Colorimeter, using Light Filter Primary B_2, Reducing Filter 5. Standard deviation: 30 with Reducing Filter 5-10. Other types of spectrophotometers may be used if desired.

(2) *Total Nitrogen*—Can be determined by the Kjeldahl Method. (Method 1) U. S. P. XIV, page 740, using about 300 mg. of atropine methylnitrate, previously dried at 105° C. for 3 hours and accurately weighed, and using 0.1 N acid and alkali. Each cc. of 0.1 N acid is equivalent to 1.401 mg. of nitrogen—not less than 7.5% and not more than 7.8% of nitrogen is found.

(3) *Atropine Methylnitrate Tablets*—Can be assayed by adaptation of the method described in the U. S. P. XIV, page 282, based on the technique suggested by Bandelin.[17]

Standard Atropine Methylnitrate Solution—Weigh accurately 25 mg. atropine methylnitrate, previously tested for purity as under IV (a) and (b) and assayed according to the procedure outlined in

IV (c), methods 1 and 2. Dry sample at 105° C. for 3 hours, and dissolve it in water to make exactly 50 cc.

Weigh a counted number of not less than 20 atropine methylnitrate tablets, and reduce them to a fine powder without appreciable loss. Weigh accurately a portion of the powder, equivalent to about 10 mg. of atropine methylnitrate, and shake it with 10 cc. of water at frequent intervals during 30 minutes. Filter under reduced pressure through a sintered glass crucible into a test tube placed in the suction flask under the filtering funnel, and wash under suction with several small portions of water. Transfer the contents of the test tube to a 25 cc. volumetric flask, add water to make exactly 25 cc. and mix well. Pipette into test tubes exactly 10 cc. each of the standard atropine methylnitrate solution and of the dilution of the sample. To each add 1 cc. of 20% sulfuric acid, and 2 cc. of ammonium reineckate T. S.; shake gently but well, and allow to stand at about 25° for one hour. Filter through a sintered glass crucible with suction, using portions of the filtrate to transfer the precipitate completely to the filter, and wash it with three 2 cc. portions of ice cold water. Completely dissolve the precipitate by pouring over it 1 cc. portions of acetone with the application of suction, receiving the solution in a 10 cc. volumetric flask or glass stoppered cylinder. Add acetone to make exactly 10 cc., mix well and determine the absorbancy of each solution in a Lumetron Photoelectric Colorimeter using Light Filter M515. Standard deviation: 30 with Reducing Filter 10. Other types of spectrophotometers may be used if desired.

Summary

Atropine methylnitrate is inferior to atropine as a mydriatic or anhidrotic. It possesses comparable activity as an antispasmodic for smooth muscle relaxation. Although pharmacological toxicity reports differ, it is apparent that atropine methylnitrate is much less toxic clinically than atropine, and can be safely administered in much larger doses, thereby attaining greater spasmolytic control.

A method for preparing atropine methylnitrate is outlined, with tests for identity and purity and quantitative assay procedures.

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ANTIHISTAMINIC DRUGS IN DENTISTRY

By Morris M. Wolfred *

THERE is a great deal of evidence to support the hypothesis that the symptomatology of clinical anaphylactic shock, allergies and sensitivities are due to the presence of histamine or a histamine-like substance. Therefore, it is not surprising to find that the symptomatic treatment of these conditions has been directed toward inhibiting or nullifying the action of histamine by the discovery of substances which antagonize the histamine effect.

Dale and Laidlaw (1) in 1910 demonstrated the role of histamine in anaphylaxis and allergy by injecting histamine into experimental animals and noting that the symptoms corresponded with anaphylactic shock. This fact, later confirmed by other workers, was followed by the work of Dragstedt and Mead (2) who showed that an animal contained enough histamine in the blood and lymph during anaphylactic shock to account for many of the symptoms. Prior to the production of anaphylactic shock, the blood and lymph was found free of histamine; therefore, it was inferred that histamine was the main causative agent. The exact mode or mechanism in anaphylaxis and allergy is still unknown, but it is suggested and maintained that histamine or a histamine-like substance is the causative agent (3). It has been postulated (4) that histamine is bound as a precursor or as an inactive form in most tissue cells of the body, its concentration in lung tissue being particularly high; the intracellular reaction between antigen and antibody or reagin reaction results in the liberation of histamine or an "H" factor. The released histamine ("H") is free to attach itself to other receptors on adjacent cells, producing damage which results in the symptoms of allergy and anaphylaxis.

The solution to the problem of relieving histaminic symptoms is two-fold: the discovery of substances which antagonize the histamine effect, and the development of non-specific methods of desensitization or increase in resistance of the organism to histamine by repeated injections of small doses.

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Hill and Martin in 1932 (5) prepared a discourse on the chemical agents which had been used for this purpose up to that time and found that none had significant or specific therapeutic value. The discovery by Fourneau and Bovet (6), Staub (7), Loew, Kaiser and Moore (8), *et al.*, that certain ethylenediamines and aminoethyl ethers were powerful antagonists of histamine provided the basis for the research that led to the specific synthetic antihistaminic agents of today.

The use of the term, antihistaminic, would lead us to classify in this category all drugs that antagonize the actions of histamine. If true, this classification would also contain the sympathomimetic amines, including epinephrine, which tend to produce pharmacological actions such as elevation of blood pressure, bronchial dilation, vasoconstriction, etc., in contrast to histamine. This is contrary to our accepted use today of the term antihistaminic, as referring to a compound that has no physiological action *per se* in therapeutic doses but will block the actions of histamine.

The accepted hypothesis of the antihistaminic drugs is that they attach themselves to the histamine receptors in the cells, blocking or preventing the attachment of the histamine released by the reagin reaction. They also prevent histamine from increasing capillary permeability and vasodilation as evidenced by a decreased erythema response. They have by themselves very little pharmacological activity and in therapeutic doses do not significantly affect a normal organism. They will produce their effect only under pathological conditions where histamine is released. A solution of histamine will not be destroyed or its action modified when mixed with an antihistaminic drug *in vitro*.

The allergic reaction to medicinal agents has been clearly demonstrated in the field of dentistry. Such drugs or agents as penicillin, streptomycin, aureomycin, sulfonamides, barbiturates, procaine, cocaine, thiamine chloride, morphine, acetylsalicylic acid, iodized oils, bromides, iodides, etc., often present conditions of sensitivity which make these substances inadvisable or difficult to use. They reveal symptomatic allergic manifestations which result in erythema, inflammation, urticaria, pruritis, edema and other histamine-like reactions. This would indicate the use of a substance that could afford symptomatic relief from drug induced sensitivity and at the same time be used as a means of prophylaxis in patients with a history of allergy.

This could be accomplished by the use of antihistaminic drugs, as confirmed in the recent literature; however, the limitations of these agents must be recognized at the same time.

The dental practitioner is often confronted by patients with common colds, hay fever, rhinitis, coryza, etc., and he is forced to either cancel the appointment or work under stress and adverse conditions. Such conditions are uncomfortable for both the patient and the dentist. The use of antihistaminic drugs can in most cases aid the situation if prophylaxis is provided prior to the appointment; they have been found particularly effective in the relief of nasal stuffiness, sneezing, lacrimation, profuse nasal discharge, allergic rhinitis, and the abolishment of symptoms of the common cold.

Bronchial asthma, an allergic condition of the respiratory tract characterized by cough, expectoration due to edema of the mucous membrane of the lungs, and paroxysmal dyspnea, is encountered frequently in a patient. One must bear in mind that drug allergies and various types of intolerances to drugs are frequently encountered with these patients and a complete history must be observed. With the use of antihistaminics the bronchial edema and cough are frequently improved, although the dyspnea is not benefited in the majority of cases. One must remember that the greatest value of the antihistaminics for the dentist is the prevention of these attacks rather than aborting or alleviating them. The antihistaminics are almost completely devoid of benefit when the asthma is complicated or induced by a respiratory infection (9). Because of such factors, the use of a supplement of parenteral aminophylline added to an antihistaminic is looked upon favorably (10, 11, 12, 13).

Sensitivities to amalgams (14), plastics, denture base materials, mouthwashes, toothpastes, denture cleaners, gums, lipsticks (15), etc., have been reported. They may occur of low incidence, but they should never be underestimated by the dentist. An accurate and complete history and a series of contact tests are essential to diagnosis. Many of these conditions may be alleviated or controlled by antihistaminic drugs until proper diagnosis can be made. Non-specific allergies of the mouth also fall into this category.

The anaesthetic properties of several antihistaminic agents have been reported (16, 17, 18, 19, 20), and a hypothesis indicates that a histamine-like substance plays a role in the activation of the pain receptors. Mosely (19) reports satisfactory anaesthesia of the oral

and pharyngeal mucosa prior to gastroscopy, and Bulbring and Wajda (16) demonstrated a longer lasting anaesthetic effect than procaine. Dutta (21) and Dunlop (22) have reported several as being more potent than procaine. The anaesthetic properties of these agents may be utilized by injection, topical application, compresses and in ointments.

A practitioner may occasionally encounter toxic manifestations such as vertigo, drowsiness, headache, gastro-intestinal irritation with the use of these antihistaminic drugs, but it has seldom been necessary to discontinue these drugs because of their effects. Few blood dyscrasias or tissue toxicity in therapeutic doses have been demonstrated, and cumulative and addictive properties have not been reported.

A vast number of antihistaminic drugs have been presented to the practitioner within a short period of time. One must bear in mind that these drugs are mainly of the structure:

$$R_1 - X - (CH_2)_n - N < \begin{matrix} R_2 \\ R_3 \end{matrix}$$

R_1—a. single aryl or heterocyclic group.

b. single aryl and a single heterocyclic group.

c. two aryl groups.

d. two heterocyclic groups.

e. single alkyl and a single aryl or heterocyclic group.

X—an oxygen, nitrogen or carbon atom in the above position.

R_2 and R_3—are generally short chain simple alkyl groups (methyl or ethyl).

Emphasis must be placed on the fact that while all antihistaminic drugs have in common an antihistaminic effect, various members of the above example formula may exhibit different clinical pictures as to effectiveness, dosage and untoward effects. Therefore, the results observed with one type of antihistaminic is not representative of all the antihistaminics, and each must be tried individually as a given structure. It will be to the benefit of the practitioner to select a given number of these drugs from the above representative groups and incorporate them in his future practice of dentistry.

Summary

The accepted hypothesis of drug sensitivities, allergies, and anaphylactic shock indicates that the release of histamine from a bound precursor is the main cause of histamine-like reactions.

Chemical agents which have been postulated to attach themselves to histamine receptors, blocking the attachment of histamine, are known as antihistaminic drugs. When used in the absence of histamine they do not produce a pharmacological response.

The dental practitioner will find the antihistaminic drugs of utmost importance in the treatment of drug sensitivities, many of the allergies, and conditions which result in the occurrence of histamine-like reactions.

The cancellation or extension of a dental appointment by a patient displaying a profuse nasal discharge, stuffiness, sneezing, lacrimation, allergic rhinitis, etc., may be avoided by the prophylactic administration of an antihistaminic drug prior to the appointment.

A patient with a sensitivity induced bronchial asthma may in most cases be controlled by the use of aminophylline and an antihistaminic drug.

Sensitivities due to amalgams, plastics, denture base materials, mouthwashes, and dental cleansers can be treated successfully with these drugs.

The antihistaminic agents can be utilized for their anaesthetic value by topical or parenteral application, compresses and ointments.

These agents consist mainly of the type formula:

$$R_1 - X - (CH_2)_n - N<\begin{matrix}R_2\\R_3\end{matrix}$$

All antihistaminics do not display the same activity and dosage but vary according to patient and type and degree of sensitivity. They should be tried individually, and the dental practitioner should employ several different types according to his patients' needs.

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STUDY ON THE HETEROTRANSPLANTATION OF EHRLICH CARCINOMA IN RELATION TO ANTI-BODY FORMATION *

By Julian L. Ambrus, Clara M. Ambrus, Joseph W. E. Harrisson and Howard Cravetz

PAUL EHRLICH (1) long ago described the inoculation of tumors into species other than the regular host, where they may grow for a short period of time. However, regression soon follows.

Putnoky (2) succeeded in partially adopting the Ehrlich mouse-tumor to rats, i. e., this tumor could be transferred to adult rats, but it regressed about 10 days after inoculation. By transferring the tumor to other rats before the 10th day, the mouse tumor was transferred from rat to rat for more than 7 years. The antigenicity of the tumor did not change during this time. Hall (3) recently described an unidentified mouse cancer which, injected subcutaneously, takes in young rats of 3-5 weeks of age, but regresses spontaneously later on.

Murphy and Sturm (4) and Shirai (5) were able to graft heterologous tumors into the brain. Greene and Murphy (6) demonstrated that heterologous tumor transplantation is possible into the anterior chamber of the eye. Murphy (7) succeeded in transplanting mouse and rat tumors into the chorioallantoic membrane and Taylor and associates (8) into the yolk sac of chick embryos.

Clemmesen (9) described the temporary growth of Crocker mouse sarcoma in rats after previous irradiation with X-rays.

In the present study Ehrlich ascites carcinoma was used. (For reviews on this tumor see (10, 11).) The tumor was carried in the abdominal cavity of Swiss mice. The tumor cells are free-swimming and multiply in the ascitic fluid without forming solid tumors. The number of cells present in the ascitic fluid can easily be counted in a hemacytometer and the percentage of inflammatory cells established in a blood smear, stained according to the method of Papanicolau (12). From these data, the number of tumor cells in a cubic millimeter can be calculated.

In a recent study, susceptibility of different strains of mice to this tumor was studied (13). The tumor could not be transplanted to adults of other species.

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We have found, however, that subcutaneous injections into Sherman rats ranging from 6 days to 2 weeks of age often resulted in tumor takes, but these tumors regressed as the animal grew older.

In a series of experiments we subcutaneously inoculated 25 million cancer cells together with 0.2 ml. of 30% sheep-red blood cell suspension into 30 one week old rats. Tumor growth was roughly ascertained by palpation every day, and 0.1 ml. of blood was taken at the end of each week by heart puncture. Although the individual rats exhibited large variations, there could be established a certain correlation between the appearance of antisheep blood hemagglutinins and the regression of the tumors. It is probable that with the maturing of the antibody forming system of the young animals, antibodies are formed against the heterologous proteins (mouse cancer cells and sheep red cells) which results in destruction of the mouse-cancer cells. Ehrlich mouse-tumor grown in rats may be readily re-transplanted by the subcutaneous or intraperitoneal routes into adult Swiss mice, where it grows without regression.

In several instances mouse tumors growing in young rats were removed, ground, incubated at 37° C. for 4 hours with anti-mouse rabbit serum or anti-rat rabbit serum. This material was then injected intraperitoneally into Swiss mice.

The anti-mouse serum-treated cancer cells did not take, while the anti-rat serum-treated cancer cells resulted in takes developing into typical ascitic tumors.

We conclude from these results that although the Ehrlich mouse-tumor may be transplanted into young rats and therein grow for a period, nevertheless, it remains essentially composed of mouse-tumor cells.

Summary

1. Regression of Ehrlich mouse carcinoma, transplanted into young rats, sets in at the same period when heterohemagglutinin formation appears toward antigenic stimuli. This may be regarded as a further evidence that heterotransplantation of tumors is possible in young animals only because of the immaturity of the antibody forming apparatus.

2. The mouse tumor seems to retain its original antigenicity while growing in young rats.

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Treatment of Herpes Zoster. Marsh, W. C. *U. S. Armed Forces Med. J. 1:*1045 (1950). Herpes zoster is evidenced by hyperesthesia, itching or pain, and the development of tense, grouped vesicles along the course of the affected nerves. Many courses of treatment have been suggested, with varying results. The author has proposed daily intramuscular injections of Protamide, a colloidal solution of a processed and denatured proteolytic enzyme obtained from the glandular layer of fresh hog stomach by controlled pepsin reactions. Only patients experiencing pain were treated in this series. No local or systemic treatment was given to the 31 patients other than the 1.3 cc. daily intramuscular injections of Protamide. Most patients received from 3 to 8 injections with one receiving 22 injections.

The author reported that good to excellent results were obtained in 28 of the patients. The thousands of previous patients treated with other methods acted as controls for this series. The relief of pain was superior to that obtained with other therapy employing such substances as pituitrin, thiamine hydrochloride, autohemotherapy, sodium iodide, and roentgen therapy. Vesicles and crusts disappeared more rapidly with the new treatment. No local or systemic reactions from Protamide were observed, and there was a noted absence of pain in administration.

SODIUM CARBOXYMETHYLCELLULOSE AS A SUBSTITUTE FOR ACACIA

By C. J. Cole and C. Lee Huyck*

SODIUM carboxymethylcellulose ** is a white granular, odorless and tasteless powder which is soluble in water. It is known to the trade as cellulose gum, sodium cellulose glycolate, carboxymethocel, collocel and CMC.

It has been suggested as a substitute for gelatin, glue, gum arabic, agar agar, tragacanth and cherry gum as an emulsifying agent for oil in water emulsions (1). For sake of brevity this material will be referred to as CMC. When tested on laboratory animals (2) such as white rats, guinea pigs and dogs, CMC was found to be non-toxic.

The purpose of this investigation was to find out to what extent a solution of CMC can be substituted for mucilage of acacia in pharmaceutical preparations.

Experimental

In substituting low viscosity sodium carboxymethylcellulose for acacia the first step was to determine the absolute viscosity of 1% low viscosity sodium CMC and 1% acacia solution at 20° C. by use of the Ostwald viscosimeter. Absolute viscosity was changed to kinematic viscosity by the formula kinematic viscosity equals absolute viscosity divided by density. Kinematic viscosity is recorded in Table I.

Specific gravity was determined by pycnometer method.

TABLE I

CALCULATIONS OF THE KINEMATIC VISCOSITY OF 1% ACACIA AND 1% LOW VISCOSITY SODIUM CMC SOLUTION

	Absolute Viscosity	Specific Gravity	Kinematic Viscosity
1% Acacia Solution	1.938	1.0040	1.93
1% Low Viscosity Sodium CMC Sol.	8.80	1.0039	8.76

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** Sodium carboxymethylcellulose was furnished by Hercules Powder Co., Wilmington, Delaware.

From this table it can be seen that 1% low viscosity Sodium CMC is approximately 4.5 times as viscous as the acacia solution. Approximately 22% as much low viscosity Sodium CMC as acacia would be necessary.

An acacia and a sodium CMC mucilage were prepared according to the above data and were found to have approximately the same viscosity. After two weeks the official acacia mucilage decomposed while the sodium CMC mucilage showed no signs of decomposition.

Emulsion of Liquid Petrolatum USP (3) was prepared with acacia and the low viscosity sodium CMC as emulsifying agents by the continental method. The emulsion prepared with acacia by the USP method was successful and stable but the emulsion with the sodium CMC was unsuccessful. An attempt was made to make the emulsion by the English method from the corresponding amount of mucilage of low viscosity CMC followed by homogenization but it was dark in color and the oil was not emulsified. It was decided that a surface active agent must be added to make an emulsion.

In the presence of 0.1 Gm. to 0.2 Gm. castile soap per two fluid ounces of emulsion to act as surface active agents successful mineral oil emulsions were prepared by the English method. The addition of 0.2 Gm. castile soap produced such a thick emulsion that it would not pour from the bottle. The procedure used to make two fluid ounces of the emulsion was as follows: Make a mucilage of 1.65 Gm. of low viscosity sodium CMC and 10 cc. of water in a mortar. 0.1 Gm. castile soap was dissolved in about 3 cc. of water and mixed with the mucilage. The vanillin was dissolved in about 3.6 cc. alcohol and mixed with 6 cc. of simple syrup. This solution was diluted with the remainder of the water to be used. The liquid petrolatum was then added in small portions to the sodium CMC soap mixture with trituration. The alcohol syrup mixture was added alternately with the liquid petrolatum to keep the emulsion at the right consistency.

In comparing the stability of the two emulsions, the emulsion with sodium carboxymethylcellulose creamed sooner than the official emulsion. After four weeks storage, however, both emulsions were rapidly dispersible upon shaking.

Discussion

Sodium CMC along with a small amount of surface active agent such as castile soap or sodium lauryl sulfate can be used as a substi-

tute for acacia in making mineral oil emulsions, but there would be no particular advantage in its use. Although sodium carboxymethylcellulose has some physiological action, there would not be sufficient amount present to make any claims for it in this preparation.

Summary

1. Solution of sodium carboxymethylcellulose is more permanent than mucilage of acacia in that it requires no preservative.

2. Solution of sodium carboxymethylcellulose requires the addition of a surface active agent in order that it may be substituted for acacia in mineral oil emulsions.

3. Solution of sodium carboxymethylcellulose of the same viscosity as mucilage of acacia does not have sufficient surface acting properties to make an emulsion.

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LABORATORY NOTES

Marking Mice

IN our breeding colony, mice are identified by a system based on punching the ears and cutting fingers. With this system, it is possible to identify animals to six figure numbering. However, certain types of work require a system which permits quick identification without handling or touching and sometimes from a considerable distance. This is accomplished by using a marking system wherein different stains are applied to the fur at various body locations. Picric acid has long been used for this purpose and is especially suitable as it combines with the protein and remains visible for several months. Fuchsin (red) is also useful, although not as durable. Mice of C_3H (brown) and dba (leaden) may be marked with picric acid, although not so distinctly as white mice.

Neither of these marking procedures is applicable to the C_{57} or C_{58} strains, which are black. The following method was devised for use upon black and brown strains:

To 4 parts of 30% Hydrogen Peroxide, 1 part of 10% solution of ammonium hydroxide is added. This mixture is then used to spot the animal fur. Black mice develop brownish red spots easily distinguishable for about one month.

J. W. E. Harrisson; Julian Ambrus and Howard Cravetz

The Effect of Histamine Desensitization During Pregnancy

HISTAMINE desensitization has been used for a long time in the treatment of allergies and related diseases. During experiments with histamine desensitization some of our rats, receiving increasing doses of 5-100 mg./100 gm., subcutaneously (sc.) during a period of

one month became pregnant and threw regular and healthy litters. The mothers developed histamine resistance in this period which was measured by the decrease and final disappearance of the body temperature reducing effect of 5 mg./100 Gm. histamine sc., as observed daily before the administration of the desensitizing dose of histamine.

In 31 new born rats (1 day to 1 week) from desensitized mothers and 26 new born ones from control mothers the subcutaneous LD_{50} of histamine was determined using the formula of Behrens (1). It was found in both cases to be 825 mg./Kg., which indicated that no desensitization of the embryo occurred during intrauterine life. This may be due to the high histaminase content of the placenta (review of literature (2)). It should be noted that, in spite of the high histaminase content of plasma of pregnant animals (2) no significant change could be observed in the course of desensitization of pregnant females as compared to non-pregnant ones, nor was there any difference in the histamine sensitivity of pregnant and non-pregnant control animals.

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SELECTED ABSTRACTS

Motion Sickness. Harbert, F., and Schiff, M. *U. S. Armed Forces Med. J. 1:979* (1950). The authors define motion sickness as that disability produced by acceleration and deceleration or rotation in any plane. The various theories on the causes of motion sickness were discussed with the conclusion presented that motion sickness is not the result of stimulation of a single organ. Rather, it is the result of a break in accommodation by the spinal and medullary centers from continual and unusual stimuli arising in many body organs. The senses mostly involved, in order of decreasing importance, are probably vestibular, proprioceptive, visual, and others such as offensive odors. Sensations from these sources are correlated and integrated in cerebellar, medullary and spinal centers. When these centers are continuously bombarded with unusual stimuli, particularly when these stimuli are inconsistent, a point is finally reached when they cause more than proper reflexes. At this point the break in accommodation brings about the symptoms of motion sickness, often quite suddenly. The authors also pointed out that psychogenic causes play an important part in the causation of motion sickness.

General hygienic measures will help reduce the symptoms in many cases. Elimination of nervous tension and purposeful physical activity are helpful. In cases of seasickness lying down with eyes closed will reduce both visual and skeletal reaction to stimulation. Since the symptoms are characteristic of overstimulation of the parasympathetic nervous system, rational therapy involves the use of atropine, hyoscine, and hyoscyamine. The barbiturates are useful adjuvants since they reduce apprehension and worry as well as the sensitivity of the medullary centers.

Recently the antihistamine, Dramamine, has shown great promise in the prophylactic and therapeutic treatment of motion sickness. The drug is apparently nontoxic with a minimum of side effects. Recent experiments indicate that the drug acts upon the central nervous system above the level of the vestibular nuclei but not the labyrinth. The authors stated that they had obtained relief of vertigo in patients with Ménière's disease and of the postoperative vertigo following the fenestration operation.

Insulin and Electric Convulsion Therapy of Rheumatoid Arthritis. Kersley, G. D., Mandel, L., Jeffrey, M. R., and Desmarais, M. H. L. *Brit. Med. J.* No. 4684:855 (1950). It had previously been shown that insulin hypoglycemia provoked the liberation of adrenalin and that the adrenal cortex may be stimulated in this way, either directly in hypophysectomized animals or indirectly by stimulation of the pituitary with liberated adrenalin. Therefore, the authors determined to treat a pilot series of patients with active rheumatoid arthritis with insulin and with electric convulsive therapy.

A series of 40 cases of rheumatoid arthritis were treated by insulin hypoglycemia 5 times a week for 3 or 4 weeks. The reaction was normally interrupted 3 hours after the dose of insulin. Of this series 22 patients showed marked clinical improvement, 9 slight improvement, 8 no change, and 1 deterioration. In the patients showing improvement such change was evident within a week of starting treatment. Laboratory findings showed that the serum potassium was lowered at the height of hypoglycemia but had risen again at the time of maximum eosinopenia, 4½ hours later. Urinary uric acid excretion was significantly raised during treatment in most cases but there was no increase in the neutral 17-ketosteroids. The sedimentation rate was not significantly changed.

Eleven patients were treated with electric shock therapy with an average of 5 shocks each. Three of these patients showed marked improvement, 3 slight improvement, and 5 no change.

The authors emphasized that the use of insulin hypoglycemia should not be looked upon as a treatment for rheumatoid arthritis at the present time. Further control and follow up is required. The authors are also seeking further information on the matters of potassium excretion, fluid retention, correlation of results with ACTH sensitivity, and the value of intermittent treatment.

Aureomycin Effective in the Treatment of Anemia. Lichtman, H., Ginsberg, V., and Watson, J. *Proc. Soc. Exp. Biol. Med.* *74*:884 (1950). Aureomycin proved to be effective in the treatment of Addisonian pernicious anemia in 4 of 5 patients in relapse and in one patient with nutritional macrocytic anemia. The possible

mode of action of the antibiotic in such cases was discussed by the authors. The reduction of bacteria in the intestines may remove a hemolytic toxin at the same time. Such a reduction in bacteria may permit the growth of other organisms which produce pteroylglutamic acid or other hematopoietic substances. A recent study revealed that *B. coli* had a marked affinity for vitamin B_{12} and it was thus thought that perhaps the reduction in the intestinal flora by aureomycin may increase the amount of vitamin B_{12} available for the patient. A last possibility considered was that aureomycin may have a hematopoietic action independent of its antibiotic action, but this seems unlikely since the one patient given the antibiotic intravenously showed no response whatsoever.

Two patients received 2 and 3 Gm. orally a day of aureomycin for 32 and 40 days, respectively. One patient was given 3 micrograms of vitamin B_{12} a day but showed no pronounced improvement until 3 Gm. of the antibiotic a day were added. Then the response was better than with the antibiotic alone. Lean meat proved to be necessary in the diet of one patient before a response was obtained with a daily dose of 2 Gm. orally of the antibiotic. Three micrograms of vitamin B_{12} a day, and, later, pteroylglutamic acid, produced no additional improvement when added to the therapy of the patient with nutritional macrocytic anemia. The one patient given aureomycin intravenously for 20 days in doses of 600 mg. a day showed no response whatsoever.

The authors stated that the bone marrow of all 5 of the improved cases had returned to normal at the conclusion of the treatment period. The reticulocyte response was irregular and the clinical response was not as rapid as that obtained with vitamin B_{12} or liver extract given parenterally. No neurological reactions were noted.

Variation in Dosage Schedule and Its Effect on Therapy With Penicillin. Eagle, H., Fleischman, R., and Musselman, A. D. *Am. J. Med. 9:*280 (1950). Variations in the dosage schedule employed have a pronounced effect upon the results obtained in therapy with penicillin. The method of administration may cause

a variation of more than a hundredfold in the curative dose of penicillin, according to the results found in studies of β-hemolytic streptococci infections in mice and rabbits, in type I and type III pneumococci infections in mice and in *T. pallidum* infections in rabbits. For example, the curative dose in type I pneumococcal infections in mice was 256 mg. per Kg. on a single dose schedule but only a total of 3.4 mg. per Kg. when divided into 4 injections at 3 hour intervals. However, it was found that these widely varying but equally effective doses provided the effective concentration of penicillin for the essentially same aggregate period of time.

The interval between injections during which penicillin levels are below the effective concentration is also an important factor. For a time after penicillin levels have fallen below effective concentrations some organisms have been found to be more susceptible to the host defenses while other organisms simply do not multiply. However, they all begin to multiply again after a time. Therefore, if the next injection is delayed too long the remultiplication largely counteracts the effect of the preceding treatment. The length of the penicillin-free interval may be longer without seriously affecting the therapeutic effect of the preceding injections when the organisms are relatively slow multiplying, the period of contact with effective serum levels of penicillin had been relatively long, the organisms recover relatively slowly from the toxic effects of penicillin, and when the number of organisms surviving the previous treatment was relatively small.

Adequate dosage with penicillin has at least two aspects, the concentration attained at the focus of infection and the total time for which that concentration is provided. A serum concentration of 2 to 4 times greater than that required to kill the organisms at the maximum rate *in vitro* was usually sufficient to produce the optimum therapeutic effect *in vivo*. Massive doses providing several hundred times this dose did not further accelerate the rate of the action of penicillin, but the action did proceed just as rapidly. Penicillin administered in absorption-delaying vehicles should be just as effective as multiple injections of aqueous solutions, providing the serum level obtained is greater than that necessary to kill the particular organism at the maximum rate. The total time for which an effective concentration must be maintained at the focus of infection depends upon the rate at which the particular organism can be killed by the antibiotic and upon the number of organisms present

in the host. A problem which often confronts therapy in human beings is that, although adequate serum levels are obtained for what should be an adequate period of time, a cure is not always obtained. One possible explanation of this phenomenon may be that bacteria are only susceptible to the bactericidal action of penicillin in an environment conducive to growth and multiplication. Thus, in a condition in which the organisms are multiplying very slowly because of the lack of nutrient material the penicillin may be, paradoxically, inactive.

The Therapeutic Use of Chloramphenicol in Pertussis. Khalil, A. and Abdin, Z. H. *Lancet 259:*307 (1950). An oral preparation of chloramphenicol in a gum emulsion syrup was given to 25 patients with early cases of whooping cough. An initial dose of 50 mg. per Kg., given over a period of about 45 minutes, was followed by a like dose each day divided into 6-hourly fractions. This dose was continued until the paroxysms were broken up or until they had become quite mild. This time interval was usually about 7 days and was followed by treatment for an additional 7 to 10 days with one half of the previous dosage.

Nine of the patients were in the catarrhal stage of the disease. Of these, 2 ceased to cough within 4 days of the beginning of treatment, 3 continued to have a cold-like cough for 1 or 2 weeks, 3 developed a typical but mild spasmodic cough which lasted for 4 to 6 days and was followed by a bronchitis-like cough for an additional 1 to 2 weeks, while the last patient in this group developed a severe spasmodic cough which lasted for 17 days. The apparent failure of treatment in this one case was thought to be traceable to diarrhea which lasted for more than a week at the beginning of treatment.

Sixteen of the patients were in the early paroxysmal stage of the disease when treatment was begun. Of these, 15 showed improvement in the frequency and severity of paroxysms and a cessation of them within 9 to 17 days. A bronchitis-like cough followed for an additional 1 to 2 weeks.

The authors stated that they had little trouble with vomiting by patients provided the drug was taken on an empty stomach.

BOOK REVIEWS

Water in the Physiology of Plants. By A. S. Crafts, H. B. Currier, and O. R. Stocking. 1949, Waltham, Mass., U. S. A. Published by the Chronica Botanica Company.

After a short preface, written by the authors, acknowledgments, a list of text illustrations, and a list of tables, the book contains ten chapters. Each chapter starts with an introduction and ends with a summary. At the end, there is a bibliography, an author and a subject index.

The book deals with many facts in the realm of physics, which are unknown to the average botanist, though they are extremely important. It is, therefore, very helpful for Chronica Botanica to make these facts available to the botanist.

Chapter I is a short introduction.

Chapter II has the title "Structure of Water." The chapter starts with earlier theories, describes the "Hydrol-Theory," and later work on it. It reports conception of normal and polar liquids, modern studies, X-ray studies and finally about current research.

Chapter III—Properties of Solutions. This chapter describes the interrelations of the properties of solutions, the forces between atoms and molecules, molecular interaction and water-binding, hydration and mobility of ions.

Chapter IV—Osmosis and Osmotic Pressure. This chapter explains the refinement of the osmotic pressure law and causes for non-ideal behavior of solutions.

Chapter V—The Mechanism of Osmosis. In the introduction to this chapter the terms osmosis, osmotic pressure, diffusion, diffusion pressure, diffusion pressure deficit, turgor and turgor pressure are explained. Then the kinetic basis of osmosis, osmosis in liquid systems, the mechanics of osmosis, the solvent and solute pressure theories, calculation by indirect methods, evaluation of diffusion pressure, the diffusion pressure of the solvent are discussed.

Chapter VI—Water as a Plant Component—Intracellular Distribution of Water. This chapter is more botanical than previous ones. We find here the description of the anatomy of cells, water content, binding forces, water of cell walls, protoplasmic

water, water in vacuoles, methods for determining water partition and, finally, equilibrium between phases.

Chapter VII—The Osmotic Quantities of Plant Cells. This chapter gives a description of the quantities and of their interrelations. Membranes and permeability, permeability to solutes, permeability to water, permeability of cell walls, osmotic pressure, methods of measuring osmotic pressure in plants, the plasmolytic method, limitations of the plasmolytic method, plasmolytic method experimental procedure, further uses of plasmolysis, the plasmometric method, cryoscopy, expression of sap, the cryoscope, physical principles, freezing-point determination, vapor pressure methods, osmometric methods, other methods for osmotic pressure, the magnitude and variation of osmotic pressure in plants, diffusion pressure deficit, methods of measuring DPD (diffusion pressure deficit), the magnitude and fluctuation of DPD values, turgor of plant cells, measurement of turgor and intercellular movement of water are discussed.

Chapter VIII—Active Cell Water Relations. This chapter deals with the water within the cell, including water which is held in the protoplasm. The following are discussed: evidence from plasmolytic and cryoscopic measurement, interpretation of sap expression data, plasmolytic behavior of cells, cryoscopy of tissues and their equilibrium bathing solutions, auxin and water uptake, measurement of diffusion pressure deficits, evidence from studies of frost and drought resistance, evidence from animal physiology, relations to solute accumulations, relations to other plant functions.

Chapter IX—Uptake and Movement of Water in Plants. This chapter deals also with the rising of the sap in the plant. The following subjects are discussed: water absorption, active absorption, passive absorption, methods of estimating the availability of water, water movement, cohesion theory, cohesion and adhesion, liquid continuity in the xylem, dye penetration, freezing of stems, transpiration experiments, direct observation of xylem, tension developed in the xylem, direct measurements, potometer experiment, suction tension measurements, newer methods of estimating tensions in xylem, rate of water movement through plants, quantity of material moved and area of transport, indicators (salts, dyes, radioactive tracers, heat), variations in the

rate of sap flow, water balance and redistribution, and translocation of solutes.

Chapter X—Water Loss and Water Retention. This last chapter deals with the loss of water, as it takes place for instance with the transpiration, and water absorption, as it is done mainly by the root system. The following items are described: laws of evaporation, evaporation from a free water surface, evaporation from tubes, factors affecting evaporation from free water surfaces of uniform shape and area (solutes, temperature, dryness of the air, atmospheric pressure, wing velocity), transpiration, methods of measuring transpiration, expression of results, cuticular transpiration, fluctuations in the rate of transpiration, internal factors affecting transpiration, wall structure, physical resistance to water movement, osmotic properties, internal surface, stomatal number and distributions, methods of measuring stomatal openings, genetic factors, stomatal regulation of transpiration, effect of mineral nutrients on transpiration, influence of disease, sprays, dusts and waxes of transpiration rate, physiological effects of water deficits, subaqueous transpiration.

The book is a very good source of information in plant physiology.

THEODOR P. HAAS

Biological Actions of Sex Hormones. By Harold Burrows, C. B. E., Ph. D. Second Edition, 615 pages, 1949. Cambridge University Press, London and New York. $8.50.

It is encouraging that in such a rapidly advancing field as sex hormones, a standard reference text is revised and made available as promptly as this one.

The first edition in 1945 was well received. This second edition deserves the same consideration. The text is divided into six major portions, covering the gonadotrophins, the gonadal hormones, androgens, estrogens, progestins and sex hormones of the adrenal cortex. Each of these divisions is thoroughly and completely detailed and with a very good bibliography.

This book is to be recommended as a reference text to all workers and students in this field.

M. A. GERSHENFELD, M. D.

The Thyroid Hormones and Their Actions. By G. Mansfeld, M. D. Translated by E. Pulay, Original published in 1943. English Edition, 151 pages, 1949. Fredrick Muller, Ltd. Great Britain. Price 24 shillings.

Unfortunately, six years have elapsed between the original edition in German (1943) and the English translation. Thus, while the author presents some interesting data and original experiments concerning thyroid function, the latter apparently have not been repeated by other investigators or checked by newer and recently introduced methods.

This book is not intended for and is not recommended to the casual student of the thyroid as a standard or reference text (despite its title), but should prove of interest to all who concern themselves with studies in anemia, oxygen metabolism, temperature regulation and thyroid physiology.

M. A. Gershenfeld, M. D.

Industrial Microbiology. By Samuel Cate Prescott, Sc. D., and Cecil Gordon Dunn, Ph. D., Second Edition, 923 pages, 124 illustrations, 1949. McGraw-Hill Book Company, Inc., New York. Price $8.50.

Since the time of appearance of the first edition of this book in 1940, much more of the significance and value of fermentative procedures has become known. The authors have thoroughly revised the previous edition to include the latest data on many of the available fermentation products with special emphasis given to methods of cultivating the organisms, to production media and to manufacturing processes. New sections describing the most recent development in the field have been included. With the presentation in a volume as this of a chapter covering 100 pages on antibiotics, the second edition is a timely publication.

This volume, although encyclopedic, retains its value as an authoritative work. It should prove to be a most valuable aid to all interested in industrial microbiology. The reviewer, recognizing

the great usefulness of this work, is presenting the following suggestions for consideration by the authors in future revisions.

The volume should include all known practical fermentative methods. For instance nothing is mentioned in the second edition concerning baking and the production of bread, cocoa, chocolate, tea and Vitamin B_{12}. The few remarks on cellulose fermentation and curing of tobacco should be expanded. These and others should be considered. In this volume such information is desired and this new material judiciously selected can be included by reducing the amount of space allotted to a consideration of yeast, molds, etc., and merely giving adequate references concerning the latter. In the present edition, only 3 pages are allotted to bacteria and references are not included at the end of the chapter (Chapter XI). Sixty pages including 6 pages of references are allotted to a consideration of yeasts. Approximately twenty pages including 2 pages of references are allotted to a consideration of molds. Footnotes and references can be combined for convenience and reducing the expense in publication. Appendix X should either be extended or otherwise deleted. It certainly is inadequate for practical information on sterilization, disinfection and the testing of disinfectants. Care should be exercised in spelling, printing errors, etc. For instance, sulfuric and sulfurous are written sulphuric and sulphurous. In the index Quaternary is written Quarternary.

This book should continue to serve as an excellent volume on practical industrial microbiology.

LOUIS GERSHENFELD

"Biologie der Goethe-Zeit". Edited by Adolf Meyer-Abich, Ph.D., Hamburg. Hippokrates-Verlag Marquardt & Cie, Stuttgart, and the Chronica Botanica Co., Waltham, Mass.

It is fitting to acknowledge the part that the Chronica Botanica took in the "Goethe Year" 1949. The book, published by the Chronica Botanica together with a German publishing house, is arranged by a living German scientist, and is of great interest for the scholar, interested in history, especially in the history of biology.

The book contains seven chapters, after an introduction with the title "Goethe's Naturforschung in ihrer geistesgeschichtlichen

Gestalt" (Goethe's research in the natural sciences in its intellectual-historical form), written by Dr. Meyer-Abich:

Chapter 1: *Johann Wolfgang v. Goethe:* Ausgewahlte Schriften zur Philosophie der Morphologie und zur Allgemeinen morphologischen Biologie. (Selected writings to the philosophy of the morphology, and to general morphological biology.)

Chapter 2: *Georg Foster:** Ein Blick in das Ganze der Natur. (A look into the entity of nature.)

Chapter 3: *Alexander v. Humboldt:* Die Lebenskraft oder der rhodische Genius. (The vitality or the Rhodic genius.)

Chapter 4: *Lorenz Oken:* Entwicklung der wissenschaftlichen Systematic der Thiere. (Development of the scientific systems of the animals.)

Chapter 5: *Carl Gustav Carus:* Welches sind die Anforderungen an eine künftige Bearbeitung der Naturwissenschaften? (Which are the demands to a future treatment of the natural sciences.)

Chapter 6: *Karl Ernst v. Baer:* Welche Auffassung der lebenden Natur ist die richtige? (Which conception of the animated nature is the correct one?)

Chapter 7: *Johannes Müller:* Von dem Bedurfnis der Physiologie nach einer philosophischen Naturbetrachtung. (About the need of physiology for a philosophical view of nature.)

Each chapter has a short preface, written by Dr. Meyer-Abich.

Concluding words: Goethe's Kompensationsprincip, das erste holistische Grundgesetz der modernen Biologie. (Goethe's principle of compensation, the first holistic basic law in modern biology) is written also by Dr. Meyer-Abich.

THEODOR P. HAAS

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* Georg Forster and his father Johann Reinhold took part in the second journey of James Cook 1772-1775. The Forsters went also to India. Georg F. translated the Indian national epic "Sakontala". The latter influenced Goethe to write the dialogue before the prologue in heaven as an interlude to Faust I.

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